Scientists discover 'smart' insulin molecule

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For millions of Americans with Type-2 diabetes and inject insulin to control diabetes (with onset typically in adulthood) the associated risk of cancer is of increasing concern. Studies have demonstrated that obesity and excess insulin - whether naturally produced by the body or injected in synthetic form - are associated with an increased incidence of some common cancers.

With the release of today's study, "Supramolecular Protein Engineering - Design of Zinc-Stapled Insulin Hexamers as a Long Acting Depot," in the prestigious Journal of Biological Chemistry, a team of researchers from Case Western Reserve University School of Medicine, led by Michael Weiss, MD, PhD, Cowan-Blum Professor of Cancer Research and Chair of the Department of Biochemistry, reveals their invention of a "smart" insulin protein molecule that binds considerably less to cancer receptors and self-assembles under the skin. To provide a slow-release form of insulin, t he analog self-assembles under the skin by means of "stapling" itself via bridging zinc ions. In light of its scientific and societal importance, the publication was highlighted as a "Paper of the Week" by the editors of the journal.

"It's quite a novel mechanism. Our team has applied the perspective of biomedical engineering to the biochemistry of a therapeutic protein. We regard the injected insulin solution as forming a new biomaterial that can be engineered to optimize its nano-scale properties," says Dr. Weiss. He adds, "The notion of engineered zinc staples may find application to improve diverse injectable protein drugs to address a variety of conditions from cancer to immune deficiency."

While initially tested in diabetic rats by team member Faramarz Ismail-Beigi, PhD, professor of medicine at CWRU School of Medicine, the study of this new, self-assembling insulin will continue with approval by the National Institutes of Health toward the goal of human clinical trials.

"The goal of all drug therapies is to make therapeutic molecules more selective, in other words, more effective with less complications. We've sought to accomplish this with our engineering a new and "smarter" insulin molecule, as the hormone's primary job is to bind to the key receptors that regulate blood glucose concentration (designated the insulin receptor), not cancer-related receptors," says Dr. Weiss.

The new insulin analog exhibits reduced binding to a receptor that can drive cell growth, called the IGF receptor. Protein engineering spans both basic science and its translation to clinical care. Critical to reaching the translational goal of improved insulin therapy was an interdisciplinary team, including endocrinologist, Dr. Ismail-Beigi; biochemist, Nelson Phillips, PhD, associate professor of biochemistry; X-ray crystallographer, Zhu-li Wan, PhD, instructor in biochemistry; and receptor expert, Jonathan Whittaker, PhD, associate professor of biochemistry.

The study concludes and demonstrates, "...The potential of interfacial zinc-binding sites, introduced by design, to modify the pharmacokinetics of a protein in a subcutaneous depot. Such bottom-up control of assembly illustrates general principles of supramolecular chemistry and their application to nanobiotechnology.

"Zinc stapling of insulin exemplifies a general strategy to modify the pharmacokinetic and biological properties of a subcutaneous protein depot. The engineering of novel lattice contacts in protein crystals can thus enable control of supramolecular assembly as a therapeutic protein nanotechnology."